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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/768,788	01/30/2004	Anthony J. Berno	100/1026-10	7134

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PERLEGEN SCIENCES, INC.
LEGAL DEPARTMENT
2021 STIERLIN COURT
MOUNTAIN VIEW, CA 94043

EXAMINER	
WHALEY, PABLO S	
ART UNIT	PAPER NUMBER
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/768,788	BERNO ET AL.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *31 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3-5,7-26,28-133 and 135-138* is/are pending in the application.

4a) Of the above claim(s) *50, 51, 53, 55-63, 116 and 119-132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-26,28-49,52,54,64-115,117,118,133 and 135-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

EXAMINER'S COMMENT

In the response, filed 10/31/2006, applicant stated that the Examiner indicated the draft amendments overcame under 35 USC 101 and 35 USC 112 1st. For clarification, it is noted that the Examiner stated the proposed amendments would "likely" overcome the instant rejections.

CLAIMS UNDER EXAMINATION

Claims 2, 6, 27, 134, and 139 have been cancelled. Claims herein under examination are claims 1, 3-5, 7-26, 28-49, 52, 54, 64-115, 117, 118, 133, and 135-138. It is noted that the Examiner has included claim 117, as it was incorrectly listed as withdrawn in the previous office action. This application contains claims 50, 51, 53, 55-63, 116 and 119-132 drawn to an invention nonelected with traverse in the response filed 03/24/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied, as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

CLAIM REJECTIONS - 35 USC § 101

Applicant's arguments, filed 10/31/2006, that claim 108 is directed to statutory subject matter is not persuasive. The Examiner maintains that claims 108-115 and 117 are indeed directed to statutory subject matter for reasons set forth below. This rejection is maintained and reiterated to provide clarification.

Claims 108-115 and 117 are rejected under 35 U.S.C. 101 because these claims are drawn to non-statutory subject matter. A statutory process must include a step of a physical transformation of matter, or produce a concrete, tangible, and useful result [State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998)], [AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)].

Amended claim 108 is now directed to a method for determining a relative allele frequency for an interrogation position in a pool of nucleic acid segments. The instant claim comprises steps that do not result in a physical transformation of matter, as claimed method steps are not limited to physical steps (i.e. steps done by a user), and encompass non-physical method steps that may be practiced inside of a computer (i.e. *in-silico*). Where a claimed method does not result in a physical transformation of matter, it may be statutory where it recites a result that is concrete (i.e. reproducible), tangible (i.e. communicated to a user), and useful result (i.e. a specific and substantial). In the instant case, claim 108 does not recite a tangible result such that it is useful to one skilled in the art. For these reasons, the instant claims are not statutory.

This rejection could be overcome by amending the claims to recite that a result of the method is "displayed" or "outputted" (e.g. output to a user, a display, a memory, or another computer, etc.), or by amending the claims to include a step of a physical transformation of matter (e.g. assay). For an updated discussion of statutory considerations with regard to non-functional descriptive material and computer-related inventions, see the Guidelines for Patent Eligible Subject Matter in the MPEP 2106, Section IV.

LACK OF UTILITY

Rejection of claims 1-5, 17-49, 52, 54, 64-74, 77, 108-115, 118, 133, and 138 under 35 U.S.C. 101 have been overcome in view of applicant's amendments.

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 3, 4, 5, 7-26, 28-49, 52, 54, and 64-107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 now recites a method "for characterizing an interrogation position in nucleic acid segments collected from a case and a control group" in the preamble. It is unclear whether said

"nucleic acid segments collected from a case and control group" is intended to be a further limitation of said nucleic acid segments or an active method step (e.g. collecting). If the later, applicant is encouraged to re-write the claim using active language, as the nature of the analyte, *per se*, has no restrictive effect on the instant method. Therefore, the Examiner has broadly interpreted the claims such that they do not require an active method step of "collecting nucleic acid segments from a case and a control group." This rejection is necessitated by amendment.

Claim 1 now recites "a first sample collected from the control group of n individuals." It is unclear whether this limitation is intended to be a further limitation of said sample or an active method step (e.g. collecting). If the later, applicant is encouraged to re-write the claim using active language, as the nature of the sample, *per se*, has no restrictive effect on the instant method. This rejection is necessitated by amendment.

Claim 1 now recites "a second sample collected from the case group of m individuals." It is unclear whether this limitation is intended to be a further limitation of said sample or an active method step (e.g. collecting). If the later, applicant is encouraged to re-write the claim using active language, as the nature of the sample, *per se*, has no restrictive effect on the instant method. This rejection is necessitated by amendment. Claims 3, 4, 5, 7-26, 28-49, 52, 54, and 64-107 are rejected as they depend from claim 1.

CLAIM REJECTIONS - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 5, 7, 11-22, and 133 are rejected under 35 U.S.C. 102 (b) as being anticipated by Schork et al. (US 6,291,182; Issued Sept. 18, 2001). This rejection is necessitated by amendment.

Schork et al. teach methods, software, and apparati for determining whether a genomic region harbors a gene with a detectable trait [Abstract]. More specifically, Schork et al. teach the following aspects of the instantly claimed invention:

- First group of between 50 and 300 "trait +" (i.e. case group) individuals recruited according to their phenotypes, and a second group of "trait -" individuals (i.e. control group) [Col. 21, lines 15-25], as in claim 1.
- Calculation of differences in allele frequencies between trait + and trait – groups using biallelic markers to characterize interrogation positions associated with a phenotypic trait of interest [Col. 21, lines 25-67] and [Col. 22, lines 1-10], as in claim 1.
- Association studies based on allele frequencies from case and control groups wherein polymorphism interrogation positions are associated with Alzheimers' disease (AD) [Col. 50, Example 10], [Col. 52, lines 46-55], and output of results [Table 2], [Fig. 7], and [Ref. Claim 27], as in claims 1, 4, 5, 7, 11.

- 225 disease patients and 248 control patients, which are independent of each other [Col. 52, lines 46-55], as in claims 12, 13, 14.
- Candidate genomic regions (i.e. interrogation positions) comprising biallelic markers (i.e. SNPs) for individuals associated and not associated with detectable traits (i.e. phenotypic characteristics of interest) [Ref. Claim 1], as in claim 15 and 16.
- DNA samples labeled with fluorescein ddNTP markers [Col. 51, lines 55-65], as in claims 20 and 21.
- Pooling of genomic DNA samples, characterization of polymorphisms using sequence evaluation using software designed for detecting presence of biallelic sites (i.e. polymorphisms) among pooled fragments based on intensity ratios between peaks [Col. 46, Example 6], as in claims 17, 18, 19, 22.
- Apparati and program storage device comprising instructions for implementing the above method steps [Col. 1, lines 49-60], [Ref. Claim 39], as in claim 133.

Claim Rejections - 35 USC § 103

Claims 1, 3-5, 7, 10, 11, 15, 17-21, 29-31, 33-36, 40, 41-43, 47, 48-52, 75, 108, and 109, 111-114, 133, 135-138 are rejected under 35 U.S.C. 103(a) as being made obvious by Fan et al. (Genome Research, 2000, Vol. 10, p.853-860), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kellam et al. (Antimicrobial Agents and Chemotherapy, 1994, Vol. 38, No. 1, p. 23-30).

Applicant's arguments, filed 10/31/2006, that Fan et al. do not teach (i) determining relative allele frequencies in a case group and a control group, (ii) analyzing the relative allele

frequencies in a computer system, or (iii) outputting a result that characterizes an interrogation position as associated with a phenotypic characteristic of interest are not persuasive. Applicant's arguments that Fan et al. do not teach a method wherein the number of individuals in a case group, n, and the number of individuals in a control group, m, each independently varies between 10 and 100,000 is persuasive, therefore the rejection against claim 14 is withdrawn. This rejection is maintained and reiterated against claims 1, 3-5, 7, 10, 11, 15, 17-21, 29-31, 33-36, 40, 41-43, 47, 48-52, 75, 108, and 109, 111-114, 133, 135-138 for reasons set forth below.

Regarding (i): Applicant's arguments are directed to features of applicant's invention that are not recited in the rejected claim(s). Claim 1 has been amended and is now directed to a method "for characterizing an interrogation position in nucleic acid segments collected from a case and a control group" in the preamble. Claim 1 now also recites the step of "inputting into a computer system a first measure of relative allele frequency at the interrogation position in a nucleic acid segment derived from a first sample collected from the case group of n individuals, ..., and wherein individuals in the case group are selected based on a phenotypic trait of interest." However, the nature of the nucleic acid segment, *per se*, has no restrictive effect on the instant method. Furthermore, the instant claim does recite active methods steps directed to "determining relative allele frequencies in a case and a control group." Fan et al. teach genotyping of individuals for SNPs using perfect match (PM) probe data (i.e. case group) paired with mismatch (MM) control probe data, which serves as an internal control (i.e. control [p.858, Col. 2, ¶ 3]. Therefore, for reasons set forth above, and as the instant claims do not require an active method steps directed to determining relative allele frequencies from a case and a control

group, the Examiner maintains that Fan et al. provide implicit teaching for allele frequencies from a case group and a control group.

Regarding (ii) and (iii): The specification discloses that the "relative allele frequency" (P) for a SNP position indicates the proportion of the reference and alternate alleles at the SNP position, wherein P "could be calculated" from the concentration of the reference allele [00126]. However, this is not a limiting definition for relative allele frequency. Fan et al. teach the measurement and analysis of first, second, and third measurements of relative allele fractions (i.e. frequency) based on hybridization results from 44 individuals at two distinct SNP positions [Fig. 3 and Abstract]. Therefore, the Examiner maintains that Fan et al. indeed teaches (ii). Furthermore, Fan et al. teach the output of clustering analysis hybridization results of 44 individuals (i.e. 10-100,000) at two SNP markers [Fig. 3], indicative of individuals associated with hypertension.

Fan et al. a method for genotyping SNPs using generic high-density oligonucleotide arrays that contain thousands of 20-mer oligonucleotide tags [Abstract]. More specifically, Fan et al. teach the following aspects of the instant invention:

- Measurement and analysis of first, second, and third measurements of relative allele fractions (i.e. frequency) based on hybridization results from 44 individuals at two distinct SNP positions [Fig. 3 and Abstract], which is a teaching for the first and second measures as in instant claim 1.
- Genotyping of 44 individuals for 142 human SNPs previously identified in hypertension candidates (i.e. phenotypic characteristic of interest) [Abstract] using perfect match (PM) probe data and mismatch (MM) control probe data [p.853, Col. 2, ¶ 2], which correlates to human case and control groups as in instant claims 3, 4, 5, and 11.

- Cluster analysis of hybridization results of 44 individuals (i.e. 10-100,000) at two SNP markers [Fig. 3], as in instant claims 6 and 15.
- Allele frequency estimation for observed (i.e. unknown) versus known data based on SNPs at the interrogation position using a reference allele "C" [Fig. 5], as in instant claim 16.
- DNA data pooled in equal amounts from three groups [Fig. 5], as in instant claims 17-19.
- DNA label with detectable biotin-labeled markers [Fig. 1], as in instant claims 20-21.
- Fluorescent intensity signals from > 32,000 probe pairs based on quantification of relative allele fraction values (i.e. relative allele frequency) [Fig. 2], as in instant claim 28.
- Over 64,000 20-mer probes each occupying an area of 30 μm^2 [p.853, Col. 2, ¶ 2], which meets the limitation of instant claims 29-31 and 33-34.
- Fluorescent intensities are measured and corrected via background subtraction [p.854, Col. 1, ¶ 1 and Fig. 2], as in instant claims 35 and 36.
- Relative allele fraction values [Fig. 2(B)] and cluster analysis of hybridization results [Fig. 3], which are teachings for detection evaluation as in instant claim 39 and mismatch and perfectly complementary probes as in instant claim 40.
- Perfect match (PM) probes are paired with mismatch (MM) probes differing by a single base for hybridization-control [p.853, Col. 2, ¶ 2], which correlates to probes and reference probes with varying nucleotides as recited in instant claims 41, 42, and 47.
- Varying nucleotides at the interrogation position comprising A, C, and G [Table 1], as in instant claim 43.
- Observed versus known allele frequency estimation based on SNPs at the interrogation position using a reference allele "C" [Fig. 5], which is a teaching for the limitations of instant claim 48.

- Measurement of allele frequencies using PM and MM intensities (i.e. at least two intensity signals), as required by Specie B and recited in instant claims 52.
- Fluorescein and phycoerythrin hybridization signals (i.e. reference and alternate signals) [Fig. 2], as in instant claims 49, 50 and 52; relative allele fraction values (P) determined by calculating the log of total fluorescence intensity $(PM\text{-}MM)_{fluorescein}$ / [$(PM\text{-}MM)_{fluorescein}$ + $(PM\text{-}MM)_{phycoerythrin}$] [Fig. 2], which correlates to instant claims 49-52, 108, 109. It is noted that PM-MM intensity values are based on allele concentration [Fig. 4].
- Intensity data is corrected for background and spectral overlap [p.854, Col. 1, ¶ 1], as in instant claims 113 and 114.
- Exclusion of outliers from computed ranges of data sets [p.859, Col. 1, ¶ 1], as in instant claim 112.

Fan et al. does not specifically teach a computer-implemented method for inputting allele frequency data into a computer system, as in instant claims 1 and 133-139, phenotypic characteristic of interest directed to resistance to a therapy, as in instant claim 10, or a plurality of measures, as in instant claim 75.

Webster et al. teach computer-aided methods for analyzing nucleic acid hybridization intensities of probes sets at specific interrogation positions [0068] and monitoring gene expression [Abstract]. More specifically, Webster et al. teach the following aspects of the instantly claimed invention: In a computer system: inputting a plurality of hybridization intensities of pairs of perfect match and mismatch probes (i.e. first and second measures), as in instant claim 75, comparing (i.e. analyzing) the hybridization intensities of each pair of perfect match probes in order to generate a gene expression call of the sample nucleic acid sequence [Ref. Claim 13], which equates to steps of inputting and analyzing as in instant claim 1. Webster et al. further teach at least 2 intensity signal measurements for reference and alternate gene

expression data [Fig. 8], as required by Specie B and recited in instant claims 52 and 108, and a computer system comprising a monitor, hard drive for storing and retrieving computer code for incorporating the invention, processor [0046] and [Fig. 2], and scanner [Fig. 3], as in instant claims 133-139.

Kellam et al. teach a rapid phenotypic assay for assessment of drug susceptibility of HIV isolates to reverse transcriptase inhibitors [Abstract]. More specifically, Kellam et al. teach the following aspects of the instantly claimed invention: phenotypic characteristic of interest is resistance to HIV treatment using therapeutic agent [Abstract, Tables 2 and 3], as recited in instant claim 10. It is noted that as Kellam et al. also provides a teaching for likelihood of resistance to infection, as in instant claim 7, as high resistance to a drug correlates to an increased likelihood for infection.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the rapid phenotypic assay taught by Kellam et al. and the computer-implemented analysis method of Webster et al. with the method for genotyping SNPs taught by Fan et al., where the motivation would have been to use a high throughput computer-implemented method for genotypic and phenotypic analysis of disease [Webster et al.] with phenotypic assay better suited for complex resistance patterns in humans [Kellam et al.], resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method of Webster et al. and the rapid phenotypic assay taught by Kellam et al. with the method for genotyping SNPs taught by Fan et al. as Webster et al., Kellam et al., and Fan et al. all teach the genotypic and phenotypic analysis of data.

Claims 1, 3, 4, 5, 48, 52, 75, 77, 79, 80, 81, 83, 84, 86-90, 98, 99, 100, 103, 104, 108, 109, 111, 112, 113, 135, and 136 are rejected under 35 U.S.C. 103(a) as being made obvious by Germer et al. (Genome Research, 2000, Vol. 10, p.258-266), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-6).

Applicant's arguments, filed 10/31/2006, that Germer et al. do not teach (i) determining relative allele frequencies in a case group and a control group, (ii) interrogation positions containing a biallelic polymorphism, as claim 2 and 27 were not rejected in the previous office action. However, after further consideration, the Examiner maintains that the above arguments are not persuasive. This rejection is therefore maintained for reasons set forth below, and newly applied to claim 27.

Regarding (i) and (ii): Germer et al. clearly suggest the application of their method to association studies wherein allele frequencies are determined using case and control groups [p.256, Discussion]. Germer et al. also clearly teach a high-throughput method for determining the allele frequency of biallelic polymorphisms [Abstract], as set forth in the previous office action, and as required by claim 27. As set forth in the previous office action, Germer et al. teach a high-throughput method for determining the allele frequency of biallelic polymorphisms [Abstract], comprising the following aspects of the instantly claimed invention:

- relative allele frequency measurements for two data sets using SNP sites and fractional predetermined threshold (C_t) representing [Fig. 1] and analysis of measurements [Table 1], as in instant claim 1;
- human and mouse DNA [Abstract], as in instant claims 3, 4, and 5;

- SNP markers functionally related to a disease (i.e. phenotypic characteristics of interest) [p.263, Col. 1, ¶ 2], as in instant claim 1;
- analysis at a plurality of interrogation positions [Fig. 4], as in instant claims 77, 98, and 99; calculation of mean, standard deviation , sampling errors (i.e. cutoff values based on standard deviation), [p.262, Col. 1] and frequency distribution (<15% and >85%) [p.261, Col. 2, ¶ 3], as in instant claims 79, 80, 86, 87-90;
- threshold value of 0.1 [Fig. 1], as in instant claim 83; Calculation of allele frequency at two alleles based on difference values (ΔC) and thresholds (C_t) [Fig. 1and Equation (1)], as in instant claim 100;
- accuracy of allele frequency measurement (i.e. validation) determined by genotyping and allele frequency [Fig. 3], as in instant claims 103 and 104;
- determining relative allele frequencies for biallelic polymorphisms and comparing measured and known allele frequencies (i.e. reference and alternate) [Table 2] where frequencies represent the average of intensity values [p.261, Col. 2, ¶ 2], as in instant claims 1, 48, 52 (as required by Species B), and 108; measurements made from matched and mismatched probes [p.259, Col. 1, ¶ 2], as in instant claim 109;
- Data has been corrected for differential amplification [Table 1], as in instant claim 113.
- Input/output files comprising ASCII files prepared using an editor (i.e. another data storage device), interactive user prompt (i.e. imaging device) [p.410, Col. 1, ¶ 3], as in instant claims 135 and 136.

Germer et al. do not specifically teach a computer-implemented method for inputting allele frequency data into a computer system, as in instant claims 1, 75, and 80, 81, and 84, or trimmed means, as required by Specie C (instant claims 54 and 111).

Webster et al. teach computer-aided methods for analyzing nucleic acid hybridization intensities indicating affinity between hybridization probes and sample nucleic acid sequences, and monitoring gene expression [Abstract], as set forth above. More specifically, Webster et al. teach the following aspects of the instantly claimed invention: In a computer system: inputting a plurality of hybridization intensities of pairs of perfect match and mismatch probes (i.e. first and second measures), comparing (i.e. analyzing) the hybridization intensities of each pair of perfect match probes [Ref. Claim 13] based on difference and ratio thresholds [Ref. Claims 14 and 15], as in instant claims 1, 75, and 80, 81, and 84. Webster et al. further teach mean hybridization intensities of photon counts recorded from a cell (i.e. at least two instensity counts [0099], as required by Specie B and recited in instant claim 52; background subtraction and thresholding of intensity data [Fig. 11], as in instant claim 100, and reference and alternate gene expression data [Fig. 8], as in instant claim 108.

Kroll et al. teach robust methods for comparing measurements from gene expression data comprising normalization, mean, trimmed mean (i.e. outlier exclusion), and standard deviation [Abstract, Table 1, Table 2], as required by Specie C and recited in instant claims 54, 108, 111, and 112.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the "trimmed mean" method of Kroll el al. and the computer-implemented method of Webster et al. with the high-throughput method for determining the allele frequencies of case and control data as taught by Germer et al. [p.256, Discussion], where the motivation would have been to use a more robust method for normalizing and comparing large data sets, as taught by Kroll et al. [Abstract] and in association studies [Germer et al., p.256, Discussion], resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully using the computer-

implemented method of Webster et al. and using the trimmed mean method of Kroll et al. with the high-throughput method for determining the allele frequency of Germer et al. as all teach the analysis of gene expression data.

Claims 1, 3, 4, 5, 11, 12, 13, 17-19, 22, 23, 26, 28, 52, 64-68, 72, 75-77, 133, 135-138 are rejected under 35 U.S.C. 103(a) as being made obvious by Barcellos et al. (Am. J. Hum. Genet., 1997, Vol. 61, p.734-747), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997) and Kroll et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-6) and further in view of Xiong et al. (Am. J. Hum. Genet., 1999, Vol. 64, p.629-640).

Applicant's arguments with respect to Barcellos et al. have been considered but are moot in view of the new ground(s) of rejection.

Barcellos et al. teach a method using pooled DNA amplification of microsatelite markers to facilitate high-resolution genome screening for detection of disease loci by association [Abstract]. More specifically, Barcellos et al. teach the following aspects of the instant invention:

- DNA samples obtained from human patient samples (n=51) and control individuals (n=75) [p.735, Methods and Materials], which is a teaching for first and second samples as in instant claims 1, 3, 4, 5, and 12. As humans are animals/mammals, claims 3-5 are anticipated.
- Estimation of allele frequencies in patients and controls [p.736, Col. 2, ¶ 2] and output of results [Fig. 2], as in instant claim 1.
- Analysis of allele frequency data [p.737, Col. 2, ¶ 3 and Table 1], as in instant claim 1.

- Patients selected have hemochromatosis (i.e. phenotypic trait of interest) [p.735, Col. 2, ¶ 3], as in instant claims 6 and 10; and detection of disease-predisposing loci by association analysis [p.737, Col. 2, ¶ 1], which correlates to characterizing the interrogation position as being associated with the phenotypic characteristic of interest as in instant claim 6.
- Screening of 200 patients and 200 controls [p.741, col. 2, ¶ 1], which meets the limitation of instant claims 12 and 13.
- Pooling of patient and control DNA data and conversion to 2N allele-frequency counts for each pool size [p.736, Col. 2, ¶ 2] and labeling of samples with detectable marker as in instant claims 17-19.
- Use of pooled DNA amplification [Abstract], as in instant claim 22.
- Patient and control results using multiple oligonucleotide markers [Figs. 2, 3, and 4], as in instant claim 23.
- DNA samples obtained from mothers, fathers, and affected children and pooled separately for amplification and analysis [p.739, col. 1, ¶ 1], as in instant claim 26.
- Peak height data (i.e. signal intensity) from genotyping profiles using a dinucleotide marker (i.e. a first probe on a two-nucleotide array) [Table 1] and a measure of allele frequency based on signal intensity [Table 2], as in instant claim 28.
- Association strength determined by absolute difference between patient and control allele frequencies [p.737, Col. 2, ¶ 1], as in instant claims 64, 72.
- Goodness of fit testing to measure the degree of closeness between allele-frequency distributions [p.737, Col. 1, ¶ 3] and association strength values of 0.20 (i.e. top 20%) and 0.5 (i.e. top 5%) [Table 2], as in instant claims 64-67.

Barcellos et al. do not specifically teach characterization of interrogation positions biallelic polymorphisms, as in claim 1. However, Barcellos et al. suggest the use of biallelic markers to calculate power for highly polymorphic microsatellites [p.740, Col. 2, ¶ 1 and ¶ 3], which motivates the use of biallelic polymorphisms as in instant claim 1. Barcellos et al. also do not specifically computer-implemented method and apparatus for inputting allele frequency data into a computer system, as in instant claims 1, 52, 68, 75, 133, and 135-138, signal averaging using at least two intensity of signal measurements as required by Specie B (instant claim 52), or trimmed means, as required by Specie C (instant claims 54 and 111).

Webster et al. teach computer-aided methods for inputting and analyzing nucleic acid hybridization intensities of probes sets at specific interrogation positions [0068] and monitoring gene expression [Abstract], as applied to claims 1, 52 (Specie B) 100, 108, and 133-139 above. Furthermore, Webster et al. teach the following aspects of the instantly claimed invention: allele frequency intensity blocks comprising a multitude of intensity patterns (i.e. further first and further second measures) at different interrogation positions [0071] [Fig. 7 and 8], as in instant claims 68, 75, 76, and 77.

Kroll et al. teach robust methods for comparing measurements from gene expression data comprising normalization, mean, trimmed mean (i.e. outlier exclusion), and standard deviation [Abstract, Table 1, Table 2], as required by Specie C and as in instant claims 54, 108, 111, and 112.

Xiong et al. teach a method for mapping genes involved in genetic diseases based on allele-frequency distribution differences between patient and control populations [Abstract]. More specifically, Xiong et al. teach the characterization of a disease locus containing biallelic polymorphisms using biallelic markers and calculation of biallelic marker frequencies [p.630,

Col. 2, ¶ 2 and 3]. Xiong et al. also compare techniques using microsatellite markers and biallelic markers [Abstract].

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to combine the computer-implemented analysis method of Webster et al., the trimmed mean technique of Kroll et al., and the use of biallelic markers taught by Xiong et al. with high-resolution genome screening of case/control data as taught by Barcellos et al., where the motivation would have been to use a high throughput computer-implemented method for genotypic and phenotypic analysis of disease [Webster et al.] resulting in the practice of the instant claimed invention. Further motivation for using biallelic markers to characterize interrogation positions is provided by Xiong et al., who teach that biallelic markers are ideal for population-based mapping [p.630, Col. 1, ¶ 3]. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method of Webster et al. and the high-resolution genome screening method of Barcellos et al. as both teach method of genomic analysis using allele frequency intensity data sets. One of skill in the art would have had a reasonable expectation of successfully using the trimmed means technique of Kroll et al. and the high-resolution genome screening method of Barcellos et al. as Barcellos et al. teach exclusion of data [Table 4] and statistical analysis of data.

Claims 78-83 are rejected under 35 U.S.C. 103(a) as being made obvious by Barcellos et al. (Am. J. Hum. Genet., 1997, Vol. 61, p.734-747), in view of Webster et al. (US 2002/0183933, Filed: Mar. 28, 1997), Kroll et al. (2002), and Xiong et al. (1999), as applied to claims 1, 3, 4, 5, 11, 12, 13, 17-19, 22, 23, 26, 28, 52, 64-68, 72, 75-77, 133, 135-138, above, in further view of MathWorld (http://mathworld.wolfram.com/Pairedt-Test.html, © 1999 CRC Press LLC, p. 1-2) and The 2002 County Loan Rate Calculation Procedure (2002, p.1).

Applicant's arguments with respect to Barcellos et al. regarding claims 78-83 have been considered but are moot in view of the new ground(s) of rejection.

Barcellos et al., Webster et al., Kroll et al, and Xiong et al. make obvious a computer-implemented method and system using pooled DNA amplification for genome screening, as set forth above.

Webster et al. further teach obtaining probe intensity values from a biological sample (i.e. common experimental condition) [0185], as in instant claim 78; calculating the mean values for intensity data obtained from experiments [Fig. 19], as in instant claims 52 (Specie B) and 80; and analyzing different based on user-defined thresholds [Fig. 19] [0145], which is a teaching for variable threshold values as in instant claims 81- 83.

Barcellos et al., Webster et al., Kroll et al., and Xiong et al. do not teach a pair t-test or calculation of an Olympic Average, as in instant claims 78 and 79.

The MathWorld website teaches a method for determining the paired t-test, as in instant claim 79. The 2002 County Loan Rate Calculation Procedure teaches the calculation of Olympic Averages of data, as in instant claim 79.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to combine the computer-implemented method of Barcellos et al., Webster et al., Kroll et al. , and Xiong et al. with the data analysis methods as taught by MathWorld and The 2002 County Loan Rate Calculation Procedure, where the motivation would have been to remove outliers from the data set to improve the degree of closeness between allele-frequency distributions [Barcellos et al., p.737, Col. 1, ¶ 3]. One of skill in the art would have had a reasonable expectation of successfully using the computer-implemented method made obvious

by Barcellos et al., Webster et al., Kroll et al., and Xiong et al. with the Olympic Average and paired t-test as all teach the statistical analysis of data.

CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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